REMARKS

I. Interview

Applicant agrees with the Interview Summary mailed October 26, 2010 regarding the interview conducted October 21, 2010.

II. Amendments

Claims 27, 28 and 47-50 have been canceled. Claim 11 has been amended to recite "therapeutically effective amoiunt of spongosine. Claims 19 and 21 have been amended to be consistent the recitation of a "human subject" in claim 11. Claims 53-63 have been added. No new matter has been added.

III. Present Claims

The present claims are drawn to methods for treating pain with spogosine. Applicant suprisingly found that spongosine can be safely used to treat pain in human patients. As the specification explains at page 2, certain A1 adenosine receptor agonists have been found have analgesic activity and certain A2 adenosine receptor agonists have been found anti-inflammatory activity. However, as also explained at page 2 of the specification, A1 receptor agonists are known cause bradycardia and A2 adenine receptor agonists are known cause vasodilatation leading to hypotension and tachycardia. For these reasons, adenosine receptor agonists, e.g., spongosine, were commonly considered to have limited usefulness in treatment of pain. Despite these teachings, which would discourage one from investigating adenosine receptor agonists, particularly spongosine, which was shown by Ueeda et al. have dangerous side effects, for treatment of pain, Applicant discovered that spongosine can be used to safely and effectively treatment pain in human patients. As will be seen from the accompanying declaration of Dr. Richardson, spongosine has undergone a clinical trial for treatment of pain associated with diabetic neuropathy.

IV. Rejections Under 35 U.S.C. §112, first paragraph

Claims 47-50 were rejected for lack of enablement. Claims 47-50 have been cancelled. Claims 11-14, 16, 17, 19-31 and 47-52 were rejected for lack of enablement. The Examiner stated that while the specification enables for treatment of pain with spongosine or with the combination of spongosine and gabapentin, the specification does not enablee treatment "with any other mixtures of spongosine and another analgesic agent as disclosed in claims 27 and 28."

Applicant has cancelled claims 27 and 28. Claims 11-14, 16, 17, 19-26, 51 and 52 are method of treatement claims that do not recite the use of an analgesic agent other than spongosine. These claims recite a method that comprises administration of spongosine to human subject. Because of the open language of the claims, they do not exclude treatment of the human subject with other therapeutic agents. These claims are enabled as are the other pending claims.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. §112, first paragraph be reconsidered and withdrawn.

V. Rejections Under 35 U.S.C. §112, second paragraph

Claims 19 and 21 were rejected as indefinite for not being of proper dependent form. Claims 19 and 21 have been amended to be of proper dependent form.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. §112, second paragraph be reconsidered and withdrawn.

VI. Obviousness-type double patenting

Claims 11-14, 16, 17, 19-31, and 47-52 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-16 of U.S. Patent No. 7,759,321. Applicant will address this rejection appropriately upon notification that there are otherwise allowable claims in this application.

Claims 11-14, 16, 17, 19-31, and 47-52 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 13-24 of U.S. Serial No. 10/547,454 (now claims 1-12 of U.S. Patent No. 7,790,698). Applicant will address this rejection appropriately upon notification that there are otherwise allowable claims in this application.

The Examiner stated that claims 11-14, 16, 17, 19-31, and 47-52 conflict with claims 13-24 of U.S. Serial No. 10/547,454 (now claims 1-12 of U.S. Patent No. 7,790,698). Applicant disagrees with the Examiner's assesment. The claims in U.S. Patent No. 7,790,698 are directed to treatment of inflammation while the present claims are directed to treatment of inflammation.

VII. Anticipation Rejection under 35 U.S.C. § 102(b)

Claims 11-14, 16, 17, 19-31 and 47-52 were rejected under 35 U.S.C. § 102(b) as being anticipated by Bartlett et al. (*J. Med. Chem.* 24:947-954, 1981). The Examiner stated that Bartlett et al. discloses administration of spongosine to treat carrageenan-induced inflammation. The Examiner argued that this treatment must have inherently resulted in the suppression of pain.

Bartlett et al. does not describe administration of spongosine to a human subject, as required by claim 11. Thus, irrespective of whether the administration of spongosine to rats at a level that reduced inflammation resulted in inherent treatment pain, Bartlett et al. cannot anticipate any of the pending claims, all of which depend directly or indirectly from claim 11, which now recites treatment of a human subject.

In view of the forgoing, Applicant respectfully requests that the rejections under 35 U.S.C. § 102(b) be reconsidered and withdrawn.

VIII. Obviousness Rejection under 35 U.S.C. § 103(a)

Bartlett et al. and Herrick-Davis et al.

Claims 11-14, 16, 17, 19-31 and 47-52 were rejected under 35 U.S.C. § 103(a) as being obvious in view Bartlett et al. and Herrick-Davis et al. (*European Journal of Pharmacology*, 162:365-369, 1989).

The Examiner stated that Herrick-Davis et al. discloses that a variety of adenosine analogues that are known in the art to be adenosine receptor agonists and have been found to be analgesic agents with efficacy comparable to morphine. The Examiner argued that one of the compounds tested, 2-chloroadenosine (CADO), is a close structural relative to spongosine. The Examiner argued that it would have been obvious "to conclude that compounds very closely analogous to CADO disclosed to be a potent analgesic by Herrick-Davis et al. to be consistent with an analgesic effect of spongosine as disclosed by Bartlett et al. in the treatment of an inflammatory response." The Examiner argued that one of ordinary skill in the art would have been motivated to combine these references because both references are directed to disclosures of the analgesic effects observed following the administration of 2-substituted analogues of adenosine, including spongosine.

Applicant respectfully traverses this rejection.

Even assuming spongosine exhibited properties similar to CADO, one would avoid its use in treatment of humans

Even if one were to assume that CADO and spongosine have similar properties, one would not be motivated to use spongosine for treatment of pain in humans.

This is because Bartlett et al. teach that at a dose at which spongosine reduced inflammation by just 25%, blood pressure dropped by a striking 41% and heart rate by 25%. Clearly, such side effects would not be even remotely tolerable in the treatment of pain in humans. Thus, one skilled in the art would not consider using spongosine for treatment of inflammation, pain or any

other condition even if one assumed that spongosine had analgesic properties similar to those of CADO.

Moreover, Bartlett et al. suggest that the harmful side effects observed with adenosine analogues consistently accompany anti-inflammatory activity: "The muscle relaxant, hypothermic, and hypotensive effects of 1-methylisoguanosine, as well as a number of the analogue, were accompanied by a decrease in heart rate. **None of the analogues investigated had any selectively of action whereby the bradycardia [reduced heart rate] could be removed or reduced while maintaining the other pharmacological effects**." (Bartlett et al. at 950; emphasis added). Given the detrimental side effects observed by Barlett et al. and given that the side effects are observed with several adenosine analogues that have anti-inflammatory activity, one of ordinary skill in the art would not be motivated to use spongosine to treat pain in humans. Indeed, one skilled in the art would endeavor to avoid the use of spongosine.

Because one would not consider using spongosine for treatment of any condition in a human patient, the present claims are not *prima facie* obvious in view of the teachings of Bartlett et al. and Herrick-Davis et al.

For the forgoing reasons, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

Applicant surprisingly found that spongosine can be used to safely treat pain and can do so at a dose that gives rise to a plasma concentration below the Kd for the adenosine receptor

Even if were prima facie obvious to administer spongosine to a human subject to treat pain, which it is not, Applicant has demonstrated unexpected results sufficient to rebut any conclusion that the presently claimed methods are *prima facie* obvious. These results are outlined in the specification at paragraph 0015 and are supported by the Declaration of Peter Richardson under 37 C.F.R. § 1.132, enclosed herewith.

As the specification explains at paragraph 0005, certain A1 adenosine receptor agonists have been found have analgesic activity and certain A2 adenosine receptor agonists have anti-

inflammatory activity. However, as also explained at paragraph 0005 of the specification, A1 receptor agonists cause bradycardia and A2 adenine receptor agonists cause vasodilatation leading to hypotension and tachycardia. For these reasons, adenosine receptor agonists were commonly considered to have limited usefulness in treatment of pain.

Despite these teachings, which would discourage one from investigating adenosine receptor agonists, particularly spongosine, which was shown by Bartlett et al. have dangerous side effects, for treatment of pain, Applicant discovered that spongosine can be used to safely and effectively treatment pain in human patients. In addition, Applicant surprisingly found that spongosine can be used to treat pain even when administered at a very low dose. As the specification explains at paragraph 0015, spongosine was "effective in inhibiting pain perception in mammals suffering from neuropathic and inflammatory pain even when administered at doses expected to give concentrations well below those known to activate adenosine receptors."

Spongosine can effectively reduce pain when administered at a dosage that results in a plasma concentration that is far lower than that which would be expected to be required to activate the A1 and A2A adenosine receptors

The attached Declaration of Peter Richardson, Ph.D., under 35 U.S.C. §1.132 presents data demonstrating that spongosine can effectively reduce pain when administered at a dosage that results in a plasma concentration that is far lower than that which would be expected to be required to activate the A1 and A2A adenosine receptors.

In his Declaration, at paragraphs 3-7, Dr. Richardson describes study that found that spongosine can reduce inflammatory pain in rats when administered in a manner that achieves a steady state concentration of 13 nM or even only 7 nM, both of which are far below the Kd of spongosine for the A1 receptor and the A2A receptor, 340 nM and 1,400 nM, respectively. As Dr. Richardson explains, it appears that in certain tissues, such as epithelia, tissue damaged by physical, chemical or biological trauma, and those tissues undergoing an inflammatory response, the pH is lower than that of other tissues. The lower pH alters the binding affinity of spongosine for adenosine receptors such that spongosine is selective for the A2A adenosine receptor in such tissues. As Dr. Richardson explains, this allows the unexpected alleviation of pain and

inflammation by spongosine at a plasma concentration that is too low to activate Al and A2A adenosine receptors in other tissues thereby avoiding such negative side-effects such as bradycardia and hypotension.

As Dr. Richardson explains as paragraphs 8-11 of his declaration, spongosine was effective in inhibiting pain perception in a rat model of neuropathic pain at steady state concentrations (7 nM and 13 nM) that are far below the Kd of spongosine for the A1 and A2A receptors and this results is surprising.

In his declaration, Dr. Richardson describes a phase 2A clinical trial in which the effect of spongosine on pain associated with diabetic neuropathy was studied. In this trial, hypertensive patients with painful diabetic neuropathy were administered 7 mg of spongosine three times per day for 28 days. This treatment regime resulted in peak plasma concentrations of spongosine between 150 nM and 360 nM. In a separate study using cloned human receptors the Ki of spongosine for the A1 receptor was found to be 10,000 nM and the Kd for the A2A receptor was found to be 1,400. As Dr. Richardson explains, the treatment with spongosine resulted in a statistically significant reduction in pain compared to subjects treated with a placebo. This reduction in pain was observed at a peak plasma concentration well below the Ki of spongosine for the human A1 receptor and well below the Kd of spongosine for the human A2A receptor.

In view of the forgoing, even if the presently claimed invention were *prima facie* obvious in view of the cited references, which it is not, Applicant's unexpected results are more than sufficient to overcome the *prima facie* case. For this reason, Applicant respectfully requests that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

CONCLUSION

For the reasons set forth above, Applicants submit that the claims of the instant application, as amended herein, are in condition for allowance. Reconsideration and withdrawal of the Examiner's objections and rejections are hereby requested. Allowance of the claims is earnestly solicited.

In the event that a telephone conversation could expedite the prosecution of this application, the Examiner is requested to call the undersigned at 617.542.5070.

Respectfully submitted,

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